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Randomized phase II study (EORTC 08062) of amrubicin as single agent or in combination with cisplatin versus etoposide-cisplatin as first-line treatment in patients (pts) with extensive disease small cell lung cancer (ED SCLC)

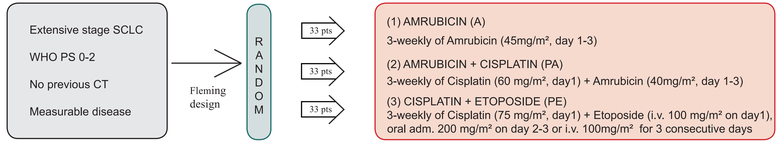
[1]O'Brien MER, [2]Jassem J, [3]Lorigan P, [4]Bosquee L, [5]Marshall E, [6]Bustin F, [7]Stigt J, [8]Dingemans AC, [9]Hasan B, [10]Van Meerbeeck JP

[1]Royal Marsden Hospital, Sutton, UK - [2]Medical University Of Gdansk, Gdansk, Poland - [3]Christie Hospital, Manchester, UK - [4]C.H.U. Sart-Tilman, Liege, Belgium -[5]Clatterbridge Centre for Oncology NHS Trust, Bebington, UK - [6]Centre Hospitalier Regional De La Citadelle,Liege, Belgium - [7]Isala Klinieken - Locatie De Weezenlanden, Zwolle, The Netherlands - [8]Academisch Ziekenhuis Maastricht, Maastricht, The Netherlands - [9]EORTC Headquarters, Brussels, Belgium - [10]Universiteit Gent, Gent, Belgium

RATIONALE OF EORTC 08062

- Background: Outcome for pts with ED SCLC remains poor, despite standard treatment with platinum and etoposide. Amrubicin is a synthetic anthracycline and a potent topoisomerase II inhibitor with less cardiotoxicity than doxorubicin[1,2,3]
- Aim: To document the activity and safety of single agent amrubicin(A), amrubicin + cisplatin (PA) and etoposide + cisplatin (PE) as first line treatment in ED SCLC
- Sample Size: With overall response rate as a primary endpoint, using a one stage Fleming design with α=0.1, β= 0.1, P_0=0.55 and P_1 = 0.8, 27 eligible pts are required in an arm. 19 responses are needed in an arm in order to declare a success

STUDY DESIGN AND PATIENT FLOW



From June 2006 to July 2009, 99 patients were randomized, 33 in each arm, by 16 institutions. The number of randomized/eligible pts who started treatment was 33/28 in A, 33/30 in PA and 33/30 in PE, respectively.

PATIENT CHARACTERISTICS*

		Treatment			Total (N=95)
		Amrubicin (N=30)	Amrubicin + Cisplatin (N=33)	Cisplatin + Etoposide (N=32)	
		N (%)	N (%)	N (%)	N (%)
Sex	Male	19 (63)	21 (64)	21 (66)	61 (64)
	Female	11 (37)	12 (36)	11 (34)	34 (37)
WHO Performance status	0	7 (23)	5 (15)	4 (12)	16 (17)
	1	19 (63)	22 (67)	23 (72)	64 (67)
	2	4 (13)	6 (18)	5 (16)	15 (16)
Age category	36 - 45 years	1 (3.3)	1 (3.0)	3 (9.4)	5 (5)
	46 - 55 years	7 (23.3)	11 (33.3)	7 (21.9)	25 (26)
	56 - 65 years	15 (50.0)	14 (42.4)	15 (46.9)	44 (46)
	66 - 75 years	5 (16.7)	6 (18.2)	7 (21.9)	18 (19)
	> 75 years	2 (6.7)	1 (3.0)	0 (0.0)	3 (3)
Presence of non-malignant associated chronic disease					
no		14 (47)	8 (24)	15 (47)	37 (39)
yes		16 (53)	25 (76)	17 (53)	58 (61)

* All pts started treatment
** Eligible pts who started treatment

DRUG DOSE INTENSITY*

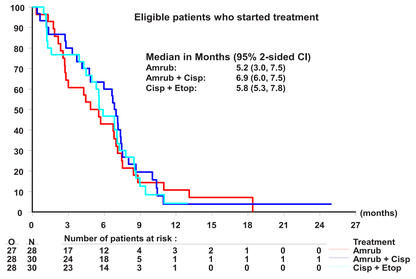
	Treatment			
	Amrubicin (N=30)	Amrubicin + Cisplatin (N=33)	Cisplatin + Etoposide (N=32)	
Amrubicin relative dose intensity (%)				
Median	91	90		
Range	46 - 101	32 - 101		
Cisplatin relative dose intensity (%)				
Median		89	89	
Range		50 - 101	18 - 104	
Etoposide relative dose intensity (%)				
Median			92	
Range			46 - 133	
Number of cycles Received				
Median	6	6	6	
Range	1 - 22	1 - 8	1 - 17	

BEST OVERALL RESPONSE**

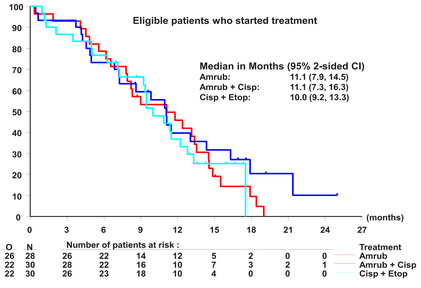
	Treatment			Total (N=88)
	Amrubicin (N=28)	Amrubicin + Cisplatin (N=30)	Cisplatin + Etoposide (N=30)	
	N (%)	N (%)	N (%)	N (%)
Best overall objective response (Investigator)				
PR	17 (61)	23 (77)	19 (63)	59 (67)
SD	6 (21)	2 (7)	4 (13)	12 (14)
PD	3 (11)	2 (7)	4 (13)	9 (10)
early death-toxicity	1 (4)	2 (7)	1 (3)	4 (5)
early death-other	0	0	2 (7)	2 (2)
not assessable	1 (4)	1 (3)	0	2 (2)

The best overall response rates and their corresponding 1-sided 90% exact Confidence Intervals are 61% (47%, 100%), 77% (64%, 100%) and 63% (50%, 100%) in A, PA and PE respectively.

PROGRESSION FREE SURVIVAL



OVERALL SURVIVAL



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SIDE EFFECTS*

Toxicity during treatment

		Treatment			Total (N=95)
		Amrubicin (N=30)	Amrubicin + Cisplatin (N=33)	Cisplatin + Etoposide (N=32)	
		N (%)	N (%)	N (%)	N (%)
WBC	Grade 3	7 (23)	10 (30)	9 (28)	26 (27)
	Grade 4	8 (27)	9 (27)	3 (9)	20 (21)
Neutropenia	Grade 3	8 (27)	7 (21)	10 (31)	25 (26)
	Grade 4	14 (47)	17 (52)	12 (38)	43 (45)
Thrombocytopenia	Grade 3	4 (13)	3 (9)	3 (9)	10 (11)
	Grade 4	1 (3)	2 (6)	0	3 (3)
Anemia	Grade 3	2 (7)	4 (12)	1 (3)	7 (7)
	Grade 4	1 (3)	1 (3)	0	2 (2)
Febrile neutropenia	Grade 3	3 (10)	4 (12)	2 (6)	9 (10)
	Grade 4	1 (3)	1 (3)	0	2 (2)
Hypotension	Grade 3	1 (3.3)	0 (0.0)	1 (3.1)	2 (2.1)
	Grade 4	0 (0.0)	1 (3.0)	0 (0.0)	1 (1.1)
Cardiac ischemia / infarction	Grade 4	0 (0.0)	1 (3.0)	0 (0.0)	1 (1.1)
Mucositis / stomatitis	Grade 3	2 (6.7)	2 (6.1)	1 (3.1)	5 (5.3)
Diarrhea	Grade 3	0 (0.0)	2 (6.1)	2 (6.3)	4 (4.2)
Vomiting	Grade 3	1 (3.3)	2 (6.1)	1 (3.1)	4 (4.2)
Neuropathy: motor	Grade 3	0 (0.0)	0 (0.0)	1 (3.1)	1 (1.1)
	Grade 4	0 (0.0)	1 (3.0)	0 (0.0)	1 (1.1)

CONCLUSION

This study shows that the combination arm, Amrubicin + Cisplatin was associated with the highest response rate. PFS and OS were similar in all arms. Based on the primary endpoint, further evaluation of this combination is warranted. All treatment groups had acceptable toxicity. Independent central review is still on going.

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2. Hanada et al. Jpn J Cancer Res. 1998;89(11):1229-1238.
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